31. (New Claim) A proteic fragment of a subtilisin-kexin isoenzyme named SKI-1, which has the amino acid sequence defined by amino acids 18 to 137 of any one of SEQ ID NOs: 2, 4 and 6, and a variant thereof, which is capable of binding with amino acids 18 to 1052 of SKI-1 in whole or in part.

32. (New Claim) The proteic fragment of claim 31, wherein said part has a molecular weight of about 14 Kda and forms a tight complex with the soluble fragment of SKI-1.

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33. (New Claim) The proteic fragment of claim 31, which is an inhibitor of SKI-1 activity.

34. (New Claim) The proteic fragment of claim 33, wherein the SKI-1 amino acid sequence that is modified to prevent further enzymatic processing in a cell expressing said protein fragment.

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35. (New Claim) The proteic fragment of claim 34, which is modified by amino acid substitution, deletion or rearrangement.

36. (New Claim) An isolated nucleic acid encoding a protein fragment as defined in claim 30.

37. (New Claim) An isolated nucleic acid encoding a proteic fragment as defined in claim 31.

38. (New Claim) An isolated nucleic acid encoding a proteic fragment as defined in claim 32.

39. (New Claim) An isolated nucleic acid encoding a proteic fragment as defined in claim 33.

40. (New Claim) A recombinant vector comprising the nucleic acid defined in claim 36.

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41. (New Claim) The recombinant vector of claim 40, which is an expression vector.

42. (New Claim) The recombinant vector of claim 41, which comprises a promoter expressible in a target cell wherein expression of said nucleic acid is desirable.

43. (New Claim) The recombinant vector of claim 42, which comprises an inducible promoter.

44. (New Claim) A recombinant host cell comprising the recombinant vector defined in claim 40.

45. (New Claim) A method of producing a proteic fragment of SKI-1 enzyme, which comprises the steps of:

culturing a recombinant host cell expressing a nucleic acid as defined in claim 36 in a cell growth and expression-supportive culture medium; and recovering said protein fragment of SKI-1 in the culture medium.

46. (New Claim) A method for cleaving a substrate for SKI-1 enzyme, which comprises the step of:

a) contacting said substrate with a SKI-1 enzyme which has 1) an amino acid sequence defined by amino acids 18 to 1052 of any one of SEQ ID Nos: 2, 4, 6 and an active variant thereof, or 2) a SKI-1 soluble fragment of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187 to 996 of any one of SEQ ID NOs: 2, 4, and 6, and a variant thereof, which is enzymatically active, or 3) catalytic part of a) or b), or 4) a complex as defined in claim 3, for a time sufficient and in conditions adequate for such cleavage to occur,

with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP).

47. (New Claim) A method for producing a protein or a peptide from a proteic precursor which is an enzymatic substrate for SKI-1 enzyme, which comprises the steps of:

a) contacting said proteic precursor with a SKI-1 enzyme which has 1) an amino acid sequence defined by amino acids 18 to 1052 of any one of SEQ ID Nos: 2, 4, 6 and an active variant thereof, or 2) a SKI-1 soluble fragment of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187 to 996 of any one of SEQ ID NOs: 2, 4, and 6, and a variant thereof, which is enzymatically active, or 3) a catalytic part of a) or b), or 4) a complex as defined in claim 32, for a time sufficient and in conditions adequate for such cleavage to occur; and

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b) recovering said protein or peptide;

with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP).

48. (New Claim) The method of claim 47, which takes place in a cell or in the presence of a cellular population and wherein step a) comprises the step of transfecting a cell with a nucleic acid expressing said SKI-1 enzyme.

49. (New Claim) The method of claim 48, wherein said cell expresses said proteic precursor or is transfected with a nucleic acid expressing said proteic precursor.

50. (New Claim) A method of inhibiting the activity of a subtilisin-kexin isoenzyme named SKI-1, which comprises the step of contacting SKI-1 with the inhibitor claim 33 or isolated nucleic acid encoding the inhibitor.

51. (New Claim) A peptide of at least 7 amino acids capable of binding to and of being cleaved by SKI-1 catalytic site, comprising the following general formula:

Arg $Xaa_1$ J$Xaa_2$ ↓ $Xaa_3$ $(Z)_nO$

wherein $Xaa_{1, 2, 3}$ and Z are any amino acid

J is an alkyl or aromatic hydrophobic amino acid

N is 1, 2 or 3

O is an acidic amino acid,

with the proviso that the peptide does not comprise the sequence Lys-Arg-Phe-Val-Phe-Asn-Lys-Ile-Glu.

52. (New Claim) A peptide as defined in claim 51, wherein $Xaa_2$ is Lys, Leu, Phe or Thr.

53. (New Claim) A peptide as defined in claim 52 which has the sequence:

$H_2N$-Val-Phe-Arg-Ser-Leu-Lys-Tyr-Ala-Glu-Ser-Asp-COOH.

54. (New Claim) A peptide as defined in claim 51 which is labelled.

55. (New Claim) A peptide as defined in claim 54 which is fluorogenic.

56. (New Claim) A peptide as defined in claim 55 which is

Abz-Val-Phe-Arg-Ser-Leu-Lys-Tyr-Ala-Glu-Ser-Asp-Tyr($NO_2$),

wherein

Abz is orthoaminobenzoic acid, and

Tyr($NO_2$) is 3-nitrotyrosine.

57. (New Claim) The use of a peptide as defined in claim 51 for monitoring the activity of a subtilisin-kexin isoenzyme named SKI-1.

58. (New Claim) The use as defined in claim 51 for screening inhibitors of a subtilisin-kexin isoenzyme named SKI-1.

59. (New Claim) The use as defined in claim 51 for screening a subtilisin-kexin isoenzyme named SKI-1.

60. (New Claim) The use of a peptide of at least 7 amino acids capable of binding to and of being cleaved by

SKI-1 catalytic site, comprising the following general formula:

Arg $Xaa_1$ J$Xaa_2$ ↓ $Xaa_3$ $(Z)_nO$

wherein $Xaa_{1, 2, 3}$ and Z are any amino acid
J is an alkyl or aromatic hydrophobic amino acid
N is 1, 2 or 3
O is an acidic amino acid,

for monitoring the activity of a subtilisin-kexin isoenzyme named SKI-1.

61. (New Claim) The use of a peptide of at least 7 amino acids capable of binding to and of being cleaved by SKI-1 catalytic site, comprising the following general formula:

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Arg $Xaa_1$ J$Xaa_2$ ↓ $Xaa_3$ $(Z)_nO$

wherein $Xaa_{1, 2, 3}$ and Z are any amino acid
J is an alkyl or aromatic hydrophobic amino acid
N is 1, 2 or 3
O is an acidic amino acid,

for screening inhibitors or substrates of a subtilisin-kexin isoenzyme named SKI-1.

62. (New Claim) The use of an inhibitor of the activity of a subtilisin-kexin isoenzyme named SKI-1 in the making of a medication for treating a disease

involving an overexpression of a SKI-1 or a SKI-1 substrate.

63. (New Claim) The use as defined in claim 62, wherein said disease is associated with any one of hypercholesterolemia, high levels of fatty acids, lipids or farnesyl pyrophosphate, liver steatosis, Ras-dependent cancer, restenosis and amyloid protein formation.

64. (New Claim) The use as defined in claim 62, wherein said inhibitor is defined in claim 31.

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65. (New Claim) A composition comprising a SKI-1 fragment as defined in claim 30.

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66. (New Claim) The use of a SKI-1 enzyme as encoded by nucleic acids to 18 to 1052 of SEQ ID NOs: 1, 3 or 5, or of a catalytic part that is unique to SKI-1 enzyme, or of an active variant thereof, the nucleic acid of the variant sharing at least 70% homology with the nucleic defined in SEQ ID NOs: 1, 3 and 5 and hybridizing therewith under stringent hybridization conditions, for cleaving a proteic precursor, with the proviso that said proteic precursor is not a sterol-regulatory element-binding protein (SREBP).

67. (New Claim) A composition comprising an SKI-1 fragment as defined in claim 31.

68. (New Claim) A composition comprising a SKI-1 fragment as defined in claim 32.

69. (New Claim) A composition comprising a SKI-1 fragment as defined in claim 33.

70. (New Claim) A composition comprising a SKI-1 fragment as defined in claim 34.

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71. (New Claim) A composition comprising a SKI-1 fragment as defined in claim 35.

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72. (New Claim) A composition comprising a nucleic acid as defined in claim 36.

73. (New Claim) A composition comprising a nucleic acid as defined in claim 37.

74. (New Claim) A composition comprising a nucleic acid as defined in claim 38.

75. (New Claim) A composition comprising a nucleic acid as defined in claim 39.

76. (New Claim) A composition comprising a recombinant vector as defined in claim 36.

77. (New Claim) A composition comprising a recombinant vector as defined in claim 37.

78. (New Claim) A composition comprising a recombinant vector as defined in claim 38.

79. (New Claim) A composition comprising a recombinant vector as defined in claim 39.

80. (New Claim) A composition comprising a recombinant vector as defined in claim 40.

81. (New Claim) A composition comprising a recombinant vector as defined in claim 41.

82. (New Claim) A composition comprising a recombinant vector as defined in claim 42.

83. (New Claim) A composition comprising a recombinant vector as defined in claim 43.

Concluded

REMARKS

Examiner Moore has informed Applicants that through a miscommunication of an amendment made during the corresponding PCT application, a full set of claims was

not originally entered in the above-identified application. This non-entry has resulted in confusion regarding claim numbering and amendment status. The Examiner has suggested that Applicants cancel all pending claims (which the Examiner has characterized as claims 1 - 29 and which comprise some of the amended PCT claims and some of Applicants' newly added claims) and resubmit an entirely new claim set renumbered beginning with claim 30. Applicants have done this.

Applicants have enclosed a Fee Transmittal sheet for the entering of the new claims. If further fees are required, please charge Deposit Account 17-0055.

Respectfully submitted,

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